CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-251

CHEMISTRY REVIEW(S)

JUL 1 1998

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-521 **ADDENDUM TO CHEM. REVIEW # 6** **REVIEW DATE: 06/26/98**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT [BC]	24-Jun-98		25-Jun-98

NAME & ADDRESS OF APPLICANT: ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

DRUG PRODUCT NAME

Proprietary:	INFASURF® Intratracheal Suspension
Nonproprietary:	Calfactant Intratracheal Suspension
USAN:	Calfactant
Code Name/#:	CLSE (name used for the drug substance prior to adopting name "calfactant")
Chem.Type/Ther.Class:	1S/601

REMARKS/COMMENTS:

This is evaluation of June 24, 1998 amendment (CMC) submitted by the applicant in support of changes implemented on January 1998 in the manufacturing process of the drug substance (new centrifugation process):

CONCLUSIONS & RECOMMENDATIONS:

This NDA application is recommended for approval from the CMC standpoint, providing that new centrifugation process implemented on January 1998 in the manufacture of drug substance will be approved *via* CMC supplement. The approval letter should specified that the drug product manufactured from the drug substance batches produced with the new process can not be marketed until approval of the supplement. Also, applicant's Phase 4 commitments (see draft letter at the end of Chem. Rev. #6) should be included.

Eugenia M. Nashed, Ph.D., Review Chemist

cc:
Org. NDA 20-521
HFD-570/Division File
HFD-570/ENashed
HFD-570/DToyer
HFD-570/GPoochikian
HFD-570/MPina
HFD-570/JSun

ACS for GP
7/1/98

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-521 **CHEM. REVIEW #** 5 **REVIEW DATE:** 05/07/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	13-MAR-95	13-MAR-95	06-NOV-95
ORIGINAL NDA (RESUBMISSION)	27-JUL- 95	31-JUL- 95	06-NOV-95
AMENDMENT [BC]	10-AUG-95	14-AUG-95	06-NOV-95
AMENDMENT [BC]	22-AUG-95	24-AUG-95	06-NOV-95
AMENDMENT [BC]	26-SEP-95	29-SEP-95	06-NOV-95
AMENDMENT [BZ]	16-OCT-95	17-OCT-95	06-NOV-95
AMENDMENT [BC]	01-DEC-95	05-DEC-95	07-DEC-95
AMENDMENT [BI]	08-FEB-96	12-FEB-96	11-MAR-96
AMENDMENT [BC]	06-MAR-96	08-MAR-96	11-MAR-96
AMENDMENT [BC]	12-APR-96	17-APR-96	19-APR-96
AMENDMENT [BC]	10-MAY-96	16-MAY-96	20-MAY-96
AMENDMENT [BI]	11-JUL-96	15-JUL-96	15-JUL-96
AMENDMENT [BZ]	19-JUL-96	23-JUL-96	23-JUL-96
AMENDMENT [BZ]	06-AUG-96	08-AUG-96	08-AUG-96
AMENDMENT [BZ]	13-AUG-96	15-AUG-96	15-AUG-96
AMENDMENT [AZ]	06-NOV-96	08-NOV-96	14-NOV-96
AMENDMENT [BZ]	14-NOV-96	18-NOV-96	14-NOV-96
AMENDMENT [BZ]	09-DEC-96	11-DEC-96	14-NOV-96
AMENDMENT [BZ]	12-FEB-97	13-FEB-97	14-FEB-97
AMENDMENT [BZ]	14-Mar-97	20-Mar-97	21-Mar-97
AMENDMENT [BZ]	07-APR-97	10-APR-97	10-APR-97
AMENDMENT [BC]*	21-APR-97	23-APR-97	21-APR-97
AMENDMENT [BL]*	21-APR-97	24-APR-97	21-APR-97
AMENDMENT [BC]*	22-APR-97	23-APR-97	22-APR-97
AMENDMENT [BC]*	24-APR-97	28-APR-97	24-APR-97
AMENDMENT [BC]*	25-APR-97		25-APR-97
AMENDMENT [BL]*	25-APR-97		25-APR-97
AMENDMENT [BC]*	29-APR-97	30-APR-97	01-May-97
AMENDMENT [BZ]*	29-APR-97	30-APR-97	01-May-97
AMENDMENT [BF]*	29-APR-97	01-May-97	02-May-97
AMENDMENT [BC]*	01-May-97	05-May-97	02-May-97
AMENDMENT [BC]*	02-May-97		02-May-97
AMENDMENT [BC]*	05-May-97		05-May-97
AMENDMENT [BZ]*	05-May-97	06-May-97	06-May-97
AMENDMENT [BL]*	06-May-97		07-May-97

* Subject of this review

NAME & ADDRESS OF APPLICANT:

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

NDA 20-521

REMARKS/COMMENTS:

This is chemist's review of the 21-Apr-97 (*CMC*), 21-Apr-97 (*Label*), 22-Apr-97 (*CMC*), 24-Apr-97 (*CMC*) 25-Apr-97 (*CMC*), 25-Apr-97 (*Label*), 29-Apr-97 (*CMC*) and 29-Apr-97 (*Label*), 2-May-97 (*CMC*), 5-May-97 (*CMC*), 7-May-97 (*CMC*) and 7-May-97 (*Carton Label*) amendments submitted by the applicant in response to the agency *CMC* comments faxed to the applicant on 17-Apr-97 (result of Chem. Rev. #4), agency *Labeling* comments faxed to the applicant on 16-Apr-97 and in response to the teleconferences with applicant on 18-Apr-97, 23-Apr-97, 24-Apr-97, 25-Apr-97, 1-May-97, 2-May-97, 5-May-97 and 6-May-97.

CONCLUSIONS & RECOMMENDATIONS:

This NDA application is approvable from the CMC standpoint providing that a detailed, updated CMC (including Method Validation) package will be submitted 180 days prior to the final (market) approval of the application and that all commitments will be fulfilled adequately by the Applicant as stated in the commitment section of this review. The approval letter should remind Applicant of all commitments and agreements resulting from Chem. Rev. #5 (see Review Notes for the List of Applicant's Commitments section).

Eugenia M. Nashed, Ph.D. Review Chemist

cc:
Org. NDA 20-521
HFD-570/Division File
HFD-570/ENashed
HFD-570/BKuzmik
HFD-570/GPoochikian
HFD-570/MPina
HFD-570/GAras
HFD-570/JSun
HFD-570/BGillespie

R/D Init by: 5/7/97

Summary of Chemistry Review

A. Drug Substance

1. Description and Characterization: **SATISFACTORY**; see Chem. Rev. #4.
2. Manufacturer: **SATISFACTORY**; see Chem. Rev. #1.
3. Synthesis/Manufacture: **SATISFACTORY**; see Chem. Rev. #5.
4. Specifications/Analytical Methods: **SATISFACTORY**; see Chem. Rev. #5.
5. Containers/Closure System: **SATISFACTORY**; see Chem. Rev. #5.
6. Stability: **SATISFACTORY**; see Chem. Rev. #5 for stability commitment - no comprehensive data on SP-B available at this time. Retest Period: 6 months, may be extended through a prior-approval supplement only.

B. Drug Product

1. Components/Composition: **SATISFACTORY**; see Chem. Rev. #4.
2. Specifications and Methods for Drug Product Ingredients: **SATISFACTORY**; see Chem. Rev. #5.
3. Manufacturer: **SATISFACTORY**; see Chem. Rev. #2.
4. Manufacturing and Packaging: **SATISFACTORY**; see Chem. Rev. #4.
5. Specifications and Test Methods: **SATISFACTORY**; see Chem. Rev. #5 for applicant's commitment to optimize method MPCT1 (foreign particulates).
6. Container/Closure System: **SATISFACTORY**; see Chem. Rev. #1.
7. Stability: **SATISFACTORY**; see Chem. Rev. #5 for stability commitment - no comprehensive data on SP-B available at this time. Expiry Period: 12 months, may be extended through a prior-approval supplement only.

C. Investigational Formulations: **SATISFACTORY**; see Chem. Rev. #1.

D. Environmental Assessment: **SATISFACTORY**; see Chem. Rev. #4.

E. Methods Validation: Methods Validation will be initiated upon submission and satisfactory review of all CMC methods.

F. Labeling: **SATISFACTORY**; see Chem. Rev. #5. Trademark will be INFASURF® ; Non-proprietary (USAN) name will be CALFACTANT.

G. Establishment Inspections: **SATISFACTORY**; see Chem. Rev. #5.

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-521 **CHEM. REVIEW #** 4 **REVIEW DATE:** 04/17/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	13-MAR-95	13-MAR-95	06-NOV-95
ORIGINAL NDA (RESUBMISSION)	27-JUL- 95	31-JUL- 95	06-NOV-95
AMENDMENT [BC]	10-AUG-95	14-AUG-95	06-NOV-95
AMENDMENT [BC]	22-AUG-95	24-AUG-95	06-NOV-95
AMENDMENT [BC]	26-SEP-95	29-SEP-95	06-NOV-95
AMENDMENT [BZ]	16-OCT-95	17-OCT-95	06-NOV-95
AMENDMENT [BC]	01-DEC-95	05-DEC-95	07-DEC-95
AMENDMENT [BC]	06-MAR-96	08-MAR-96	11-MAR-96
AMENDMENT [BC]	12-APR-96	17-APR-96	19-APR-96
AMENDMENT [BC]	10-MAY-96	16-MAY-96	20-MAY-96
AMENDMENT [BC]	11-JUL-96	15-JUL-96	15-JUL-96
AMENDMENT [BZ]	06-AUG-96	08-AUG-96	08-AUG-96
AMENDMENT [BZ]*	06-NOV-96	08-NOV-96	14-NOV-96
AMENDMENT [BZ]*	07-APR-97	10-APR-97	10-APR-97

* Subject of this review

NAME & ADDRESS OF APPLICANT:

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

DRUG PRODUCT NAME

Proprietary:	INFASURF®
Nonproprietary/USAN:	Calfactant
Code Name/#:	
Chem.Type/Ther.Class:	1S/601

PHARMACOL. CATEGORY/INDICATION: Lung surfactant replacement for treatment of Respiratory Distress Syndrome (RDS) in premature infants: prophylaxis and severe RDS.

DOSAGE FORM: Sterile liquid suspension. 210 mg of extract solids in 6 mL of 0.9 % w/v NaCl for irrigation. Recommended Dose: 3 mL/kg body weight. No preservatives. Stored refrigerated.

STRENGTHS: Complicated mixture of lipids and proteins. See Drug Product Specifications for composition and proportion of major ingredients.

ROUTE OF ADMINISTRATION: Intratracheal instillation *via* endotracheal tube.

DISPENSED: _X_ Rx ___ OTC

REMARKS/COMMENTS:

This is chemist's review of the 6-Nov-96 and 7-Apr-97 amendments submitted by the applicant in response to the Agency AE letter dated 25-Jul-96 and in response to the teleconference on 4-Apr-97.

CONCLUSIONS & RECOMMENDATIONS:

All deficiencies specified in the Chemist's Draft Letter have to be addressed adequately by the applicant, including submission of updated Method Validation package, and acceptable EERs and USAN name need to be available prior to the approval of the application. The approval letter should remind the Applicant of all the commitments and agreements resulting from Chem. Rev. #1, 2 and 3 (see Remarks/Comments and Summary of Applicant's Commitments sections).

Eugenia M. Nashed, Ph.D. Review Chemist

cc:
Org. NDA 20-521
HFD-570/Division File
HFD-570/ENashed
HFD-570/BKuzmik
HFD-570/GPoochikian
HFD-570/MPina
HFD-570/JSun
HFD-570/BGillespie

R/D Init by: GMP 4/17/97

SEP 16 1996

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-521 **CHEM. REVIEW #** 3 **REVIEW DATE:** 09/12/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	13-MAR-95	13-MAR-95	06-NOV-95
ORIGINAL NDA (RESUBMISSION)	27-JUL-95	31-JUL-95	06-NOV-95
AMENDMENT [BC]	10-AUG-95	14-AUG-95	06-NOV-95
AMENDMENT [BC]	22-AUG-95	24-AUG-95	06-NOV-95
AMENDMENT [BC]	26-SEP-95	29-SEP-95	06-NOV-95
AMENDMENT [BZ]	16-OCT-95	17-OCT-95	06-NOV-95
AMENDMENT [BC]	01-DEC-95	05-DEC-95	07-DEC-95
AMENDMENT [BC]	06-MAR-96	08-MAR-96	11-MAR-96
AMENDMENT [BC]	12-APR-96	17-APR-96	19-APR-96
AMENDMENT [BC]	10-MAY-96	16-MAY-96	20-MAY-96
AMENDMENT [BC]	11-JUL-96	15-JUL-96	15-JUL-96
AMENDMENT [BZ]*	19-JUL-96	23-JUL-96	23-JUL-96
AMENDMENT [BZ]*	06-AUG-96	08-AUG-96	08-AUG-96
AMENDMENT [BZ]*	13-AUG-96	15-AUG-96	15-AUG-96

* Subject of this review

NAME & ADDRESS OF APPLICANT:

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

DRUG PRODUCT NAME

Proprietary: INFASURF®

Nonproprietary/USAN: Calf Lung Surfactant Extract

Code Name/#:

Chem.Type/Ther.Class: 1S/601

PHARMACOL. CATEGORY/INDICATION: Lung surfactant replacement for treatment of Respiratory Distress Syndrome (RDS) in premature infants: prophylaxis and severe RDS.

DOSAGE FORM: Sterile liquid suspension. 210 mg of extract solids in 6 mL of 0.9 % w/v NaCl for irrigation. Recommended Dose: 3 mL/kg body weight. No preservatives. Kept refrigerated.

STRENGTHS: Complex mixture of lipids and proteins. See Drug Product Specifications for composition and proportion of active ingredients.

ROUTE OF ADMINISTRATION: Intratracheal instillation *via* endotracheal tube.

DISPENSED: _X_ Rx ___ OTC

REMARKS/COMMENTS:

- This is chemist's review of the (A) July 19 and Aug 13, 1996 amendments submitted by the Applicant in relation to the Agency letter of May 24, 1996 ("same drug"), and (B) August 6, 1996 amendment, Applicant's request for clarification of some of the comments contained in Agency letters dated Feb. 28 (IR) and July 25 (AE), 1996.

CONCLUSIONS & RECOMMENDATIONS:

- Chemist's comments regarding the above amendments are attached on pp. 7 and 8 of this review:
  (A) CHEMIST COMMENTS IN RESPONSE TO JULY 19 AND AUGUST 13, 1996 SUBMISSIONS ("SAME DRUG")

  and

  (B) CHEMIST COMMENTS IN RESPONSE TO AUGUST 6, 1996 SUBMISSION ("CLARIFICATION").

- All deficiencies specified in the Agency letters dated Feb. 28 (IR) and July 25 (AE), 1996 have to be addressed adequately by the applicant and acceptable EERs need to be available prior to the approval of the application.

Eugenia M. Nashed, Ph.D. Review Chemist

cc:
Org. NDA 20-521
HFD-570/Division File
HFD-570/ENashed
HFD-570/BKuzmik
HFD-570/GPoochikian
HFD-570/MPina
HFD-570/YChoi
HFD-570/BGillespie
R/D Init by: QS 9/16/96

DIVISION OF PULMONARY DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

JUL 17 1996

NDA #: 20-521 **CHEM. REVIEW #** 2 **REVIEW DATE:** 07/15/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	13-MAR-95	13-MAR-95	06-NOV-95
ORIGINAL NDA (RESUBMISSION)	27-JUL- 95	31-JUL- 95	06-NOV-95
AMENDMENT [BC]	10-AUG-95	14-AUG-95	06-NOV-95
AMENDMENT [BC]	22-AUG-95	24-AUG-95	06-NOV-95
AMENDMENT [BC]	26-SEP-95	29-SEP-95	06-NOV-95
AMENDMENT [BC]	01-DEC-95	05-DEC-95	07-DEC-95
AMENDMENT [BC]*	12-APR-96	17-APR-96	19-APR-96
AMENDMENT [BC]*	10-MAY-96	16-MAY-96	20-MAY-96
AMENDMENT [BC]*	11-JUL-96		12-JUL-96

* Subject of this review

NAME & ADDRESS OF APPLICANT: ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

DRUG PRODUCT NAME

Proprietary: INFASURF®

Nonproprietary/USAN: Calf Lung Surfactant Extract

Code Name/#:

Chem.Type/Ther.Class: 1S/601

PHARMACOL. CATEGORY/INDICATION: Lung surfactant replacement for treatment of Respiratory Distress Syndrome (RDS) in premature infants: prophylaxis and severe RDS.

DOSAGE FORM: Sterile liquid suspension. 210 mg of extract solids in 6 mL of 0.9 % w/v NaCl for irrigation. Recommended Dose: 3 mL/kg body weight. No preservatives. Kept refrigerated.

STRENGTHS: Complex mixture of lipids and proteins. See Drug Product Specifications for composition and proportion of active ingredients.

ROUTE OF ADMINISTRATION: Intratracheal instillation *via* endotracheal tube.

DISPENSED: _X_ Rx ___ OTC

CONCLUSIONS & RECOMMENDATIONS:

The outstanding CMC deficiencies/comments for the New Drug Application #20-521 are summarized in the *DRAFT OF CHEMIST'S PART OF THE LETTER*. All deficiencies have to be addressed adequately by the applicant and acceptable EERs need to be available prior to the approval of the application.

Eugenia M. Nashed, Ph.D. Review Chemist

cc:
Org. NDA 20-521
HFD-570/Division File
HFD-570/ENashed
HFD-570/BKuzmik
HFD-570/GPoochikian
HFD-570/MPina
HFD-570/MHimmel
HFD-570/YChoi
HFD-570/BGillespie
HFD-160/CVincent
HFD-510/YChiu

R/D Init by: EMN 7/17/96

Kuzmik

DIVISION OF PULMONARY DRUG PRODUCTS

FEB 19 1996

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-521 **CHEM. REVIEW #** 1 **REVIEW DATE:** 02/15/96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA*	13-MAR-95	13-MAR-95	06-NOV-95
ORIGINAL NDA (RESUBMISSION)*	27-JUL- 95	31-JUL- 95	06-NOV-95
AMENDMENT [BC]*	10-AUG-95	14-AUG-95	06-NOV-95
AMENDMENT [BC]*	22-AUG-95	24-AUG-95	06-NOV-95
AMENDMENT [BC]*	26-SEP-95	29-SEP-95	06-NOV-95
AMENDMENT [BC]*	01-DEC-95	05-DEC-95	07-DEC-95

* Subject of this review

NAME & ADDRESS OF APPLICANT:

ONY, Inc.
Baird Research Park
1576 Sweet Home Road
Amherst, New York 14228

DRUG PRODUCT NAME

Proprietary: INFASURF®

Nonproprietary/USAN: Calf Lung Surfactant Extract

Code Name/#:

Chem.Type/Ther.Class: 1S/601

PHARMACOL. CATEGORY/INDICATION: Lung surfactant replacement for treatment of Respiratory Distress Syndrome (RDS) in premature infants: prophylaxis and severe RDS.

DOSAGE FORM: Sterile liquid suspension. 210 mg of extract solids in 6 mL of 0.9 % w/v NaCl for irrigation. Recommended Dose: 3 mL/kg body weight. No preservatives. Kept refrigerated.

STRENGTHS: Phospholipids (PL): 35 mg/mL with phosphatidylcholine (PC) ≥ 19 mg/mL (no spec. for DPPC), Protein: 0.5 -1.2 mg/mL (no spec. for SP-B and SP-C).

ROUTE OF ADMINISTRATION: Intratracheal instillation *via* endotracheal tube.

DISPENSED: _X_ Rx ___ OTC

CONCLUSIONS & RECOMMENDATIONS:

This New Drug Application is not approvable, at this stage, from the chemistry standpoint. The application is lacking crucial CMC data and have numerous deficiencies that are listed in the Chemist's Part of the Draft Deficiency Letter. The above should be communicated to the Applicant as soon as possible.

cc:
Org. NDA 20-521
HFD-570/Division File
HFD-570/ENashed
HFD-570/BKuzmik
HFD-570/GPoochikian
HFD-570/MPina
HFD-570/YChoi
HFD-570/BGillespie
HFD-160/CVincent
HFD-510/YChiu
R/D Init by: GP 2/19/96

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Eugenia M. Nashed, Ph.D. Review Chemist